REMARKS

Claims 1, 3-16, 20-27, 46, 48-71, and 73 are pending in the present application. Claims 1, 20, and 59 have been amended and claims 17, 18, and 19 have been cancelled without prejudice to or disclaimer of the subject matter contained therein. New claim 73 has been added.

Method claims 20-27, 46, and 48-58 have been withdrawn. However, these claims contain all the recitations of the product claims, and must be rejoined upon allowance of the product claims. Specifically, withdrawn independent claim 20 includes all of the recitations of claim 1 and withdrawn independent claim 46 has been amended to include all of the limitations of claim 59.

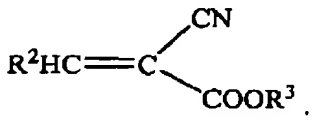
Reexamination of the application and reconsideration of the rejections are respectfully requested in view of the above amendments and the following remarks, which follow the order set forth in the Office Action.

A. Rejections under 35 U.S.C. §§ 102 and 103

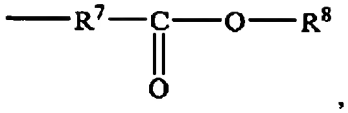
Claims 1, 3, 69, and 70 were rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,328,687 to Leung et al. For the reasons set forth below, applicants respectfully traverse the rejection.

Leung et al. discloses a biocompatible monomer composition that contains (A) at least one biocompatible monomer of formula (I) CHR=CXY, wherein X and Y are each strong electron withdrawing groups, and R is H or, provided that X and Y are both cyano groups, a C_1-C_4 alkyl group and (B) an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels. *Column 2, lines 48-60.* Leung et al. also discloses a biocompatible composition comprising (A) at least one copolymer of two monomers of formula (I) or one monomer of formula (I) and a monomer having the formula (II) CHZ=CXY, wherein X and Y are as defined above and Z is $-CH=CH_2$, and component (B). *Column 2, line 61-column 3, line 2.*

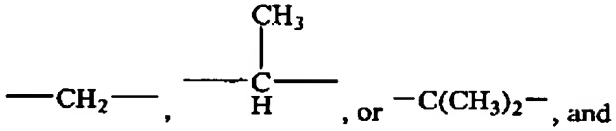
Leung et al. discloses that preferred monomers of formula (I) in the patent are alpha-cyanoacrylates, which may have the formula (III)



As disclosed, R^2 is hydrogen and R^3 may be, among other things, a group having the formula



wherein R^7 is



R^8 is an organic radical. *Column 3, lines 31-66.*

To anticipate a claim, the reference must teach every element of the claim. MPEP § 2133.

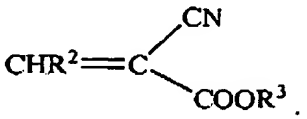
To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

Leung et al. does not teach or suggest all of the elements of claim 1 as amended. Leung et al. does not teach or suggest, as recited in amended claim 1, a biocompatible adhesive composition wherein the first and second monomer species have different absorption rates such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species. Claim 1 was amended to include the recitations from former claim 17 (now cancelled), which was not subject to the rejections.

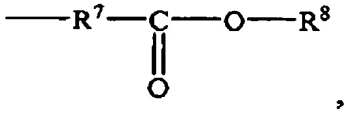
Thus, because all of the limitations of independent claims 1 (and therefore the claims depending therefrom, including claim 3, 69, and 70) are not taught or suggested in Leung et al., these claims are not anticipated by or obvious over Leung et al. Applicants respectfully request that the rejections of claims 1, 3, 69, and 70 under 35 U.S.C. §§ 102 and 103 as anticipated by or as obvious over Leung et al. be withdrawn.

Claims 1, 3-17, and 59-71 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,981,621 to Clark et al. in view of U.S. Patent No. 3,995,641 to Kronenthal et al., U.S. Patent No. 6,386,203 to Hammerslag, and EP 0965623. The rejection is moot with respect to claim 17, which has been cancelled by this amendment.

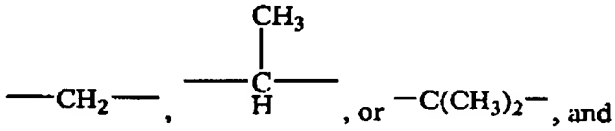
Clark et al. discloses a wound closure monomer composition comprising (A) at least one monomer, which forms a medically acceptable wound closure polymer, (B) at least one plasticizing agent, and (C) at least one acidic stabilizing agent. *Column 2, line 64-column 3, line 2.* Clark et al. discloses that preferred monomers have the formula



As disclosed, R^2 is hydrogen and R^3 may be, among other things, a group having the formula



wherein R^7 is



and R^8 is an organic radical. *Column 4, lines 7-35.* Claim 10 of Clark et al. recites a composition of claim 1 wherein the composition comprises at least two different monomers. Clark et al. also discloses that initiators that initiate polymerization and/or cross-linking of the material may be applied to a surface portion or to the entire surface of the applicator tip, including the interior and the exterior of the tip, and that the suitable initiators include cationic surfactants such as benzalkonium chloride. *Column 11, lines 18-67.*

Kronenthal et al. discloses carbalkoxyalkyl 2-cyanoacrylates. *Abstract.*

Hammerslag discloses methods and compositions for closing and sealing a wound, laceration, incision, or other percutaneous opening using an adhesive. Preferred sealing media comprise cyanoacrylates combined with fumed silica. *Abstract.*

EP 0965623 discloses an adhesive composition including a polymerizable adhesive monomer, at least one vapor phase stabilizer, and at least one liquid phase stabilizer. *Abstract.*

A *prima facie* case of obviousness has not been established because neither Clark et al., Kronenthal et al., Hammerslag, nor EP 0965623, alone or in combination, teach or suggest all the elements of independent claims 1 or 59. For example, none of the cited references, either alone or in combination, teach or suggest a biocompatible adhesive composition as recited in claim 1 comprising a combination of a first monomer species

comprising an alkyl ester cyanoacrylate that is absorbable and a second monomer species (comprising a cyanoacrylate) different from the first monomer species, wherein said first and second monomer species have different absorption rates such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species.

In addition, none of the cited references, either alone or in combination, teach or suggest a biocompatible adhesive composition as recited in claim 59 comprising a combination of at least one alkyl ester cyanoacrylate monomer, a second monomer species (comprising a cyanoacrylate) having an absorption rate different from an absorption rate of said at least one alkyl ester cyanoacrylate monomer, and a polymerization initiator or accelerator, wherein said polymerization initiator or accelerator is a quaternary amine.

As discussed above, Clark et al. discloses that preferred monomers have a formula that encompasses alkyl ester cyanoacrylates, and also includes a claim to a composition that comprises at least two different monomers. However, Clark et al. does not teach or suggest choosing an alkyl ester cyanoacrylate from the disclosed formula and combining the alkyl ester cyanoacrylate with a different cyanoacrylate monomer species having a different absorption rate such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species as set forth in claim 1.

As also discussed above, Clark et al. discloses that initiators may be applied to the applicator tip and that suitable initiators include cationic surfactants such as benzalkonium chloride. However, Clark et al. does not teach or suggest choosing an alkyl ester cyanoacrylate from the disclosed formula and combining the alkyl ester cyanoacrylate with a different cyanoacrylate monomer species having a different absorption rate and a polymerization initiator or accelerator comprising a quaternary amine as recited in claim 59.

The Examiner asserts that Hammerslag "discloses that different types of cyanoacrylates have different biodegradation rates and that cyanoacrylates can be co-polymerized with other compounds to modify the biodegradation rate" and "[a]s such, in light of the combined teachings of the prior art, it would have been well within the skill of one of ordinary skill in the art would have motivated to modify the prior art with the expectation that biodegradation rates can be modified by combining at least two different monomers having different biodegradation rates." *Office Action, page 7.* While Hammerslag does disclose that "[t]here is a wide variation in the rates ... of in vivo biodegradation of polymers made from

monomers which may be used as adhesive compounds" used in Hammerslag, and that "[t]here is a wide variation in such rates among the members of the cyanoacrylate family", Hammerslag in fact teaches away from combining a first monomer species comprising an alkyl ester cyanoacrylate with a second monomer species comprising a cyanoacrylate having a different absorption rate from the first monomer species.

Hammerslag states that "[p]olymerizable cyanoacrylates that have been cross-linked or co-polymerized **with other compounds** that may alter elasticity, modify viscosity, aid biodegradation or change some other property of the resulting material may also be used as adhesive compounds in accordance with the present invention." *Column 5, lines 22-28* (emphasis added). Thus, Hammerslag teaches that cyanoacrylates may be combined with **compounds other than cyanoacrylates** that may aid biodegradation. As an example, Hammerslag states that "polyacrylic acid having a molecular weight of 200,000 to 600,00 may be cross-linked to a cyanoacrylate to form compounds which may allow the absorbability to be coordinated with the tissue regeneration rate and may feature higher elasticity than cyanoacrylates alone." *Column 5, lines 27-32.*

In addition, Hammerslag teaches that one of skill in the art may, through scientific and medical literature and routine experimentation, "choose **a member** of the cyanoacrylate family with suitable biodegradation characteristics," but Hammerslag does not teach choosing a combination of cyanoacrylate monomers. As stated above, Hammerslag teaches using compounds other than cyanoacrylates to aid biodegradation of polymerizable cyanoacrylates. Thus, Hammerslag does not provide any suggestion or motivation to modify Clark et al. or any of the other references to reach the presently claimed invention.

Kronenthal was cited by the Examiner as teaching carbalkoxyalkyl 2-cyanoacrylates which are readily assimilated by tissues and exhibit a relatively low degree of inflammatory tissue response. *Office Action, p. 4.* EP0965623 was cited by the Examiner as teaching the combination of sulfuric acid and sulfur dioxide with free radical stabilizers for use in cyanoacrylate compositions to stabilize and enhance the shelf-life of said compositions. *Office Action, p. 4.* However, neither of these references, alone or in combination with the other cited references, teach or suggest combining an alkyl ester cyanoacrylate and a different cyanoacrylate monomer species having a different absorption rate such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species (as set forth in claim) or combining an alkyl ester cyanoacrylate with a different cyanoacrylate monomer species having a different absorption

rate and a polymerization initiator or accelerator comprising a quaternary amine (as recited in claim 59).

Therefore, independent claims 1 and 59 (and the claims depending therefrom) are not obvious over Clark et al. in view of Kronenthal et al., Hammerslag, and EP 0965623 because the elements of these claims are not taught or suggested in the cited references, alone or in combination. Applicants respectfully request that the rejection of claims 1, 3-16, and 59-71 under 35 U.S.C. § 103 as obvious over these references be withdrawn.

Claims 1, 3-17, and 59-71 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,981,621 to Clark et al. in view of U.S. Patent No. 3,995,641 to Kronenthal et al., U.S. Patent No. 6,386,203 to Hammerslag, and EP 0965623, in further view of U.S. Patent No. 3,559,652 to Banitt et al. or Collins et al. ("Biological Substrates and Cure Rates of Cyanoacrylate Tissue Adhesives", Arch. Surg. (1966), Vol. 93, pp. 428-432). The rejection is moot with respect to claim 17, which has been cancelled by this amendment.

Clark et al, Kronenthal et al., Hammerslag, and EP 0965623 are discussed above. Banitt et al. discloses a method for surgically adhering living tissues and effecting hemostasis therein by means of a rapidly polymerizing composition which comprises alkoxyalkyl 2-cyanoacrylates. *Abstract.* Collins et al. discloses that longer alkyl substituted N-alkyl-2-cyanoacrylates are less toxic and more effective in achieving hemostasis, but that methyl-2-cyanoacrylate degrades more rapidly from the body. Pages 428, 431.

A *prima facie* case of obviousness has not been established because neither Clark et al., Kronenthal et al., Hammerslag, EP 0965623, Banitt et al., nor Collins et al., alone or in combination, teach or suggest all the elements of independent claims 1 or 59.

As discussed above, neither Clark et al., Kronenthal et al., Hammerslag, nor EP 0965623, either alone or in combination, teach or suggest (1) a biocompatible adhesive composition as recited in claim 1 comprising a combination of a first monomer species comprising an alkyl ester cyanoacrylate that is absorbable and a second monomer species (comprising a cyanoacrylate) different from the first monomer species, wherein said first and second monomer species have different absorption rates such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species, or (2) a biocompatible adhesive composition as recited in claim 59 comprising a combination of at least one alkyl ester cyanoacrylate monomer, a second monomer species (comprising a cyanoacrylate) having an absorption rate different from an

absorption rate of said at least one alkyl ester cyanoacrylate monomer, and a polymerization initiator or accelerator, wherein said polymerization initiator or accelerator is a quaternary amine.

As also discussed above, Hammerslag teaches away from combining a first monomer species comprising an alkyl ester cyanoacrylate with a second monomer species comprising a cyanoacrylate having a different absorption rate from the first monomer species, and in fact teaches that cyanoacrylates may be combined with **compounds other than cyanoacrylates** that may aid biodegradation.

The addition of Banitt et al. and Collins et al. do not remedy the deficiencies of the rejection. Banitt et al. is cited by the Examiner for teaching that alkoxyalkyl 2-cyanoacrylates are biodegradable and have minimal toxicity. *Office Action, p. 8.* Collins et al. is cited by the Examiner for allegedly teaching that alkyl cyanoacrylates such as octyl 2-cyanoacrylate are more effective tissue adhesives but that the higher homologues do not biodegrade as rapidly, and that the combination of effectiveness in hemostasis inducing ability of the higher homologues and rapid biodegradation of the methyl monomer would be highly desirable in a tissue adhesive. *Office Action, p. 8.* However, neither of these references, alone or in combination with the other cited references, teach or suggest combining an alkyl ester cyanoacrylate and a different cyanoacrylate monomer species having a different absorption rate such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species (as set forth in claim 1) or combining an alkyl ester cyanoacrylate with a different cyanoacrylate monomer species having a different absorption rate and a polymerization initiator or accelerator comprising a quaternary amine (as recited in claim 59).

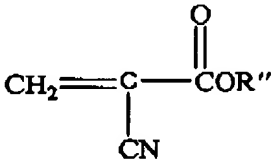
Therefore, independent claims 1 and 59 (and the claims depending therefrom) are not obvious over Clark et al. in view of Kronenthal et al., Hammerslag, and EP 0965623, in further view of Banitt et al. or Collins et al. because the elements of these claims are not taught or suggested in the cited references, alone or in combination. Applicants respectfully request that the rejection of claims 1, 3-16, and 59-71 under 35 U.S.C. § 103 as obvious over these references be withdrawn.

Claims 1, 3, 4, 8, 9, 11, 12, 14, 17, 59-62, 64, and 66-71 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No 5,998,472 to Berger et al. in view of

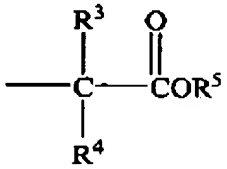
U.S. Patent No. 3,995,641 to Kronenthal et al. and U.S. Patent No. 6,386,203 to Hammerslag. The rejection is moot with respect to claim 17, which has been cancelled by this amendment.

Berger et al. discloses that the addition of a C_{10}-C_{12} alkyl cyanoacrylate ester to a C_1 to C_8 alkyl cyanoacrylate ester provides for a composition which forms a flexible cyanoacrylate polymer on mammalian skin without the need to add a plasticizer. *Column 2, lines 62-67.* Berger et al. also discloses the following:

> ... it is contemplated that the flexibility of polymeric films formed on mammalian skin from cyanoacrylate esters can be improved by the addition of a effective amount of a C_{10} to C_{12} cyanoacrylate ester wherein such cyanoacrylate esters are represented by the formula



> wherein R" is alkenyl of 2 to 10 carbon atoms, cycloalkyl groups of from 5 to 8 carbon atoms, phenyl, 2-ethoxyethyl, 3-methoxybutyl, or a substituent of the formula:



> wherein R^3 and R^4 are independently selected from the group consisting of hydrogen and methyl, and R^5 is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, alkenyl of from 2 to 6 carbon atoms, alkynyl of from 2 to 6 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl, phenyl, and phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

Column 10, line 53-column 11, line 18.

Kronenthal et al. and Hammerslag are discussed above.

A *prima facie* case of obviousness has not been established because neither Berger et al., Kronenthal et al., nor Hammerslag, alone or in combination, teach or suggest all the

elements of independent claims 1 or 59. For example, none of the cited references, either alone or in combination, teach or suggest a biocompatible adhesive composition as recited in claim 1 comprising a combination of a first monomer species comprising an alkyl ester cyanoacrylate that is absorbable and a second monomer species (comprising a cyanoacrylate) different from the first monomer species, wherein said first and second monomer species have different absorption rates such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species.

In addition, none of the cited references, either alone or in combination, teach or suggest a biocompatible adhesive composition as recited in claim 59 comprising a combination of at least one alkyl ester cyanoacrylate monomer, a second monomer species (comprising a cyanoacrylate) having an absorption rate different from an absorption rate of said at least one alkyl ester cyanoacrylate monomer, and a polymerization initiator or accelerator, wherein said polymerization initiator or accelerator is a quaternary amine.

As discussed above, Berger et al. discloses that "the flexibility of polymeric films formed on mammalian skin from other cyanoacrylate esters can likewise be improved by the addition of a effective amount of a C_{10} to C_{12} cyanoacrylate ester". *Column 10, lines 50-54.* Although the C_{10} to C_{12} cyanoacrylate ester encompasses some alkyl ester cyanoacrylates, Berger et al. does not teach or suggest choosing a combination of an alkyl ester cyanoacrylate and a different cyanoacrylate monomer species having a different absorption rate, such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species. Neither does Berger et al. teach or suggest choosing a combination of an alkyl ester cyanoacrylate, a different cyanoacrylate monomer species having a different absorption rate, and a polymerization initiator or accelerator that is a quaternary amine.

Furthermore, neither Kronenthal et al. nor Hammerslag provide any suggestion or motivation to modify Berger et al. to reach the presently claimed invention. As discussed above, Kronenthal was cited by the Examiner as teaching carbalkoxyalkyl 2-cyanoacrylates which are readily assimilated by tissues and exhibit a relatively low degree of inflammatory tissue response, and Hammerslag teaches away from combining a first monomer species comprising an alkyl ester cyanoacrylate with a second monomer species comprising a cyanoacrylate having a different absorption rate from the first monomer species, and in fact teaches that cyanoacrylates may be combined with **compounds other than cyanoacrylates** that may aid biodegradation. Neither of these references, alone or in combination with

Berger et al., teach or suggest combining an alkyl ester cyanoacrylate and a different cyanoacrylate monomer species having a different absorption rate such that an absorption rate of a faster absorbing monomer species is at least 10% faster than an absorption rate of a slower absorbing monomer species (as set forth in claim) or combining an alkyl ester cyanoacrylate with a different cyanoacrylate monomer species having a different absorption rate and a polymerization initiator or accelerator comprising a quaternary amine (as recited in claim 59).

Therefore, independent claims 1 and 59 (and the claims depending therefrom) are not obvious over Berger et al. in view of Kronenthal et al. and Hammerslag because the elements of these claims are not taught or suggested in the cited references, alone or in combination. Applicants respectfully request that the rejection of claims 1, 3, 4, 8, 9, 11, 12, 14, 59-62, 64, and 66-71 under 35 U.S.C. § 103 as obvious over these references be withdrawn.

B. Double Patenting Rejections

Claims 1, 3, 69, and 70 were rejected under the judicially created doctrine of obviousness-type double patenting as being expressly and inherently anticipated by claim 44 of U.S. Patent No. 6,662,846. Applicants believe the rejection pertains to U.S. Patent No. 6,620,846, and address the rejection on that basis.

Claims 1, 3-10, 12, 69, and 70 were rejected under the judicially created doctrine of obviousness-type double patenting as being expressly and inherently anticipated by claims 3 and 24 of U.S. Patent No. 6,605,667.

Claims 1, 3-17, and 59-71 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 64-70 of U.S. Patent No. 6,620,846 or claims 3 and 24 of U.S. Patent No. 6,605,667, each in view of U.S. Patent No. 5,981,621 to Clark et al., U.S. Patent No. 6,386,203 to Hammerslag, and EP 0965623, or U.S. Patent No. 5,981,621 to Clark et al., U.S. Patent No. 6,386,203 to Hammerslag, and EP 0965623 in further view of U.S. Patent No. 3,559,652 to Banitt et al. or Collins et al ("Biological Substrates and Cure Rates of Cyanoacrylate Tissue Adhesives", Arch. Surg. (1966), Vol. 93, pp. 428-432).

The present application and U.S. Patent Nos. 6,620,846 and 6,605,667 are commonly owned by Closure Medical Corporation. Appropriate terminal disclaimers complying with 37 CFR § 1.321(c) and obviating the double patenting rejections are enclosed herewith in order to expedite prosecution, although Applicants do not acquiesce with the rejections.

Therefore, it is respectfully requested that the double patenting rejections over U.S. Patent Nos. 6,620,846 and 6,605,667 be withdrawn.

Conclusion

For the foregoing reasons, claims 1, 3-16, 59-71, and 73 are considered allowable. A Notice to this effect is respectfully requested. Applicants also request rejoinder and allowance of claims 20-27, 46, and 48-58. If any questions remain, the Examiner is invited to contact the undersigned at the number given below.

Respectfully submitted,

HUTCHISON & MASON PLLC

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